Election/Restriction.

Applicants note with appreciation the rejoinder of Groups I and II and understand that claims 1-27, 71, and 79 are currently under Examination. Applicants further note that the restriction requirement is made final. Accordingly claims 28-70, 72-78, 80, and 81 are canceled with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Drawings.

Applicants note the Examiner's indication that the drawings are informal and acceptable for examination purposes only. Applicants will furnish formal drawings upon an indication of otherwise allowable subject matter.

Notes.

The Examiner indicated that the terms "have" or "having" were interpreted, for the purpose of examination, as closed "consisting of" in claims 1, 7, 16, and 17, and as open "comprising" in claims 2, 3, 10, and 18. Applicants have amended the claims to expressly recite consisting or comprising and thereby eliminate this ambiguity.

Priority.

Applicants note that the Examiner indicated that, for purposes of comparison with the prior art, the filing date of the present application (November 25, 1997) will be used for claims 16-27. The arguments present in this amendment are presented with respect to prior art cited against claims 16-17 assuming, *arguendo*, the November 25, 1997 priority date for these claims. Please note, however, that this is not to be construed as agreement with the Examiner's position or an admission that November 25, 1997 is the effective priority date for the subject matter of claims 16-27.

35 U.S.C. §112, second paragraph.

Claims 1-9, and 15-27 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for a variety of reasons as described below. These rejections are traversed by argument and amendment.

Claim 1.

Claim 1 was allegedly indefinite in the recitation of "an ESX transcription factor variable region polypeptide". Claim 1, as amended herein eliminates this language thereby obviating this rejection.

Claim 2.

Claim 2 was allegedly indefinite in its reference to SEQ id NO: 3 as an amino acid sequence. The Examiner alleged that SEQ ID NO: 3 in the CRF ad paper copy of the sequence listing indicate that SEQ ID NO: 3 is a nucleotide sequence. Claim 2 is amended herein to refer to SEQ ID NO: 2 which is an amino acid sequence, thereby obviating this rejection.

Claim 15.

Claim 15 was allegedly indefinite because the recitation of "said polypeptide" in line 4 could either refer to the "human EXS transcription factor polypeptide" or to the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1. Claim 15 is canceled with entry of this amendment thereby obviating this rejection.

Clam 27.

Claim 27 was allegedly indefinite because the recitation of "said polypeptide" in line 4 could either refer to the "murine EXS transcription factor polypeptide" or to the "polypeptide shown as MESX in Figure 5". Claim 15 is canceled with entry of this amendment thereby obviating this rejection.

Claim 19.

Claim 19 was allegedly indefinite because SEQ ID NOS: 16 and 17 are amino acid sequences, but are referenced in the claim as if they were polynucleotide primer sequences. Claim 19 is canceled herein thereby obviating this rejection.

Claims 16 and 27.

Claims 16 and 27 were allegedly indefinite in their reference to Figure 5. Claim 27 is canceled with entry of this amendment and claim 16 no longer refers to Figure 5. Thus this rejection is obviated.

Claims 5 and 20.

The Examiner is reminded that a claim is definite if "... **read in light of the specification** [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits. *Hybritech Inc. v Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1385, 231 USPQ 81 (Fed. Cir. 1986) cert. denied 480 U.S. 947 (1987).35 U.S.C. §112, first paragraph.

Applicants note that the specification expressly describes stringent hybridization conditions (*see, e.g.,* pages 13-14). The claim, **when read in light of the specification** reasonably apprises those skilled in the art both of the utilization and scope of the invention. Moreover, the language referring to "stringent conditions" is standard usage in the art and such language, coupled with the teaching provided in the specification, is as precise as the subject matter permits.

Moreover, Applicants note that the "The Revised Interim Written Description Training Examples" prepared by the PTO recognizes that a claim may recite "stringent hybridization" without expressly reciting particular hybridization conditions. Thus, Example 9 in these training materials provides an illustrative claim that reads:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the compliment of the sequence set forth in SEQ ID NO: 1. (Revised Interim Written Description Training Examples, Example 9: Hybridization).

The training materials after performing an analysis of this claim conclude "[t]he claimed invention is adequately described." There is no indication that the specific hybridization conditions must be expressly recited in the claim to meet the description requirement.

Thus, in accordance both with the law, *e.g.* as presented in *Hybritech*, and with the PTO's own training materials, claims 5 and 20 (and now claims 1 and 16) meet the §112, second paragraph, requirements. Accordingly, the rejection of claims 5 and 20 under 35 U.S.C. §112, second paragraph, should be withdrawn.

35 U.S.C. §112, first paragraph.

"Make and use" enablement.

Claims 1-9 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner alleged that claims 1-9 read on a nucleic acid whose only alleged use is as a probe for sequences that have no identified function and hence no utility. The Examiner's rejection is essentially an incorporation of the §101 utility requirement into §112, first paragraph. The rationale is that if an invention fails as a matter of fact to satisfy the §101 utility requirement, the invention is, in effect, inoperable and doesn't meet the §112 enablement requirement. *See, e.g. In re Zeigler*, 26 USPQ2d 1600 (Fed. Cir., 1993). Applicants respectfully traverse.

Claims 1-9, as amended herein, are directed to nucleic acids encoding ESX, expression of which is believed to be associated with various cancers. The specification clearly identifies such nucleic acids as being useful as "diagnostic markers for epithelial cancers including breast cancer" (*see, e.g.,* page 20, lines 27-28). In addition nucleic acids encoding ESX or fragments thereof are identified as useful generating proteins to raise anti-ESX antibodies "useful for immunoassays for the detection of normal or abnormal expression of ESX" which is associated with various cancers (*see, e.g.,* page 20, lines 29-30).

The claimed nucleic acids clearly have a specific, credible and substantial utility. Moreover, one of skill can routinely produce the claimed nucleic acid sequences without undue experimentation. Accordingly, Applicants have met the requirements of 35 U.S.C. §112, first paragraph, and the rejection of claims 1-9 on this ground should be withdrawn.

Description.

Claims 1, 2, 5, 7, 15, 16, 17, and 27 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleged that the claimed sequences read on an ESX gene, including promoter, and non-coding sequences and one of skill in the art would not understand that Applicant was in possession of the full scope of the claimed invention at the time the instant application was filed. Applicants respectfully traverse.

It is well settled law that the §112, description requirement does not require Applicants to have actual possession of every species within a genus to be entitled to claim the genus. If such a requirement existed, it would never be possible to issue claims to a species in light of preexisting claims to a genus.

In the instant case, one of skill would recognize that the claimed sequences can be provided in any of a number of vectors and/or clones and this is routine to those of skill in the art. One of skill in the art would readily appreciate that Applicants, at the time of filing, had possession of nucleic acid sequences comprising the particular sequences as recited in the presently pending claims.

Moreover, it is noted that Applicants performed both a chromosomal localization and Southern blotting of the ESX sequence. The ESX sequence was localized at 1q32 and was readily identified in Southern Blots (*see, e.g.,* page77). Applicants were thus, clearly in possession of nucleic acids comprising an ESX gene. Accordingly the Examiner's assertion that one of skill in the art would not understand that the Applicants were in possession of the full scope of the claimed invention that the time the application was filed is simply incorrect. Accordingly, the rejection of claims 1, 2, 5, 7, 15, 16, 17, and 27 under 35 U.S.C. §112, first paragraph, on the grounds of inadequate description is improper and should be withdrawn.

35 U.S.C. §102.

35 U.S.C. §102(e).

Claims 1, 4-16, 19-27, and 71 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Kola *et al.* (U.S. Patent 5,789,200). Applicants respectfully traverse.

Applicants note that Kola *et al.* is cited against the present application as alleged prior art under 35 U.S.C. §102(e). Applicants further note that the effective date of Kola *et al.* is allegedly October 31, 1996, while the effective priority date of the present application, particularly with respect to claims 1-14 is November 27, 1996, barely four weeks later.

Upon an indication of otherwise allowable subject matter, Applicants will provide a Declaration under 37 C.F.R. §1.131 establishing a date of invention prior to the October 31, 1996 priority date of Kola *et al.* and thereby obviating this reference as effective prior art under 35 U.S.C. §102(e), at least against claims 1-14.

With respect to claims 16-26, the Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). Claims 16-26 are directed to

> [A] nucleic acid that specifically hybridizes to a murine ESX nucleic acid under stringent conditions, wherein said murine ESX comprises a nucleic acid sequence as set forth in SEQ ID NO: 15;

or to

> a nucleic acid that encodes an amino acid sequence SEQ ID NO: 16.

Claims 16-26 are directed to a nucleic acids that encode a **murine ESX**, or that specifically hybridize to a murine ESX (*e.g.* permit one of skill to a distinguish a murine ESX from other nucleic acid sequences), while Kola *et al.* allegedly discloses only a **human** ESX. As Kola *et al.* fails to teach a murine ESX or to teach nucleic acids that **specifically** hybridize to a murine ESX, Kola *et al.* **does not** anticipate claims 16-27 and this rejection should be withdrawn.

35 U.S.C. §102(b).

Claim 1 was rejected under 35 U.S.C. §102(b) as allegedly anticipated by Filloux *et al.* (1990) *EMBO J. 9*: 4323-4329. Applicants respectfully traverse.

Claim 1 is amended herein so that it is directed to an isolated nucleic acid comprising a nucleic acid that:

> [S]pecifically hybridizes to a human ESX nucleic acid under stringent conditions;

or that

> Encodes an amino acid sequence of SEQ ID NO: 2.

According to the Examiner Filloux *et al.* discloses a polynucleotide sequence that encodes an xcp polypeptide of *Pseudomonas aeruginosa.* Such a polynucleotide sequence will hybridize to its complement, a *Pseudomonas aeruginosa* nucleic acid. The nucleic acid disclosed by Filloux *et al.* therefore **does not** specifically hybridize to a human ESX nucleic acid under stringent conditions.

Similarly, the nucleic acid disclosed by Filloux *et al.* encodes an xcp polypeptide of *Pseudomonas aeruginosa,* not the amino acid sequence of amino acids 2

through 371 of SEQ ID NO: 2 (human ESX). Filloux *et al.* thus **does not** anticipate the presently claimed invention and the rejection of claim 1 under 35 U.S.C. §102(b) should be withdrawn.

35 U.S.C. §103(a).

Claims 1-14 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Accession No: R50578, Accession No: H12657, Accession No: T27397, or Accession No: R73021 in view of Promega Corporation (Promega Protocols and Applications Guide, Promega Corporation, pages 145-153). Claim 79 was rejected under 35 U.S.C. §103(a) as allegedly obvious in light of U.S. patent 5,789,200. Applicants respectfully traverse.

The Examiner is reminded that a *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, **there must be some teaching, suggestion, or motivation to combine the references**. *In re Geiger,* 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Moreover as stated by the Court of Appeals for the Federal Circuit:

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch,* 23 USPQ 2d 1780, 1783-1784 (Fed. Cir. 1992)

In the instant case, the cited art offers no motivation to create **the presently claimed labeled nucleic acids**. The Examiner is reminded that the Genomics databases comprise literally millions of sequences any one of which can be labeled and used as a probe. There simply is no motivation to select the particular nucleic acid sequences identified by the Examiner out of all the millions of sequences in the databases for labeling with a detectable label.

To the contrary, it is Applicants discovery of the ESX gene and its association with various cancers that provides motivation to label such nucleic acids.. Lacking such teaching or suggestion in the cited references (the GenBank listings and the Promega catalogue), the only motivation supporting the obviousness rejection is Applicants own

disclosure. The Examiner's rejection thus amounts to hindsight reconstruction insufficient to support an obviousness rejection. Accordingly, the rejection of claims 1-14 were rejected under 35 U.S.C. §103(a) should be withdrawn.

Claim 79 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,789,200 (Kola *et al.*). As indicated above, upon an indication of otherwise allowable subject matter, Applicants will provide a Declaration under 37 C.F.R. §1.131 establishing a date of invention prior to the October 31, 1996 priority date of Kola *et al.* and thereby obviating this reference as effective prior art under 35 U.S.C. §102(e) and §103(a).

In view of the foregoing discussion, Applicant believes all claims now pending in this application are allowable. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 217-6021.

Express Mail Label No.:
EL710210025US

Respectfully submitted,

Tom Hunter
Attorney for Applicants
Reg. No. 38,498

Encl: 1) Petition for 3 month extension of time.
2) Change in correspondence address.

APPENDIX I

CLAIMS PENDING IN 08/978,217 WITH ENTRY OF THIS AMENDMENT

1. (Once amended) An isolated nucleic acid comprising a nucleic acid selected from the group consisting of:

a nucleic acid that specifically hybridizes to a human ESX nucleic acid under stringent conditions; and

a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2.

2. (Once amended) The isolated nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid that encodes an amino acid sequence as set forth in SEQ ID NO: 2.

3. (Once amended) The isolated nucleic acid of claim 2, wherein said nucleic acid comprises a nucleotide sequence as set forth in SEQ ID NO: 1.

4. (Once amended) The nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid having the nucleotide sequence of a nucleic acid amplified from a genomic library using the primer pairs designated by SEQ ID No. 13 and SEQ ID NO. 14.

5. (Once amended) The nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid that specifically hybridizes to a human ESX nucleic acid under stringent conditions, wherein said human ESX consists of a nucleic acid sequence as set forth in SEQ ID NO: 1.

6. The nucleic acid of claim 1, wherein said nucleic acid further comprises a vector.

7. (Once amended) The nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid that encodes a polypeptide consisting of an amino acid sequence as set forth in SEQ ID NO.: 7.

8. The isolated nucleic acid of claim 1, wherein said nucleotide sequence has a smallest sum probability of less than about 0.5 when compared to a nucleotide sequence as set forth in SEQ ID NO: 6 using a BLASTN algorithm using default parameters.

9. The isolated nucleic acid of claim 8, wherein said smallest sum probability is less than about 0.2.

10. (Once amended) The nucleic acid of claim 1, wherein said nucleic acid comprises a nucleic acid that encodes an amino acid sequence as set forth in SEQ ID NO: 12 or conservative substitutions of said amino acid sequence.

11. The nucleic acid of claim 10, wherein said nucleic acid is free of dideoxynucleotides.

12. The nucleic acid of claim 10, wherein said nucleic acid is single stranded.

13. The nucleic acid of claim 12, wherein said nucleic acid is a sense strand.

14. The isolated nucleic acid of claim 10, wherein said label is a radionuclide.

15. Canceled.

16. (Once amended) An isolated nucleic acid comprising a nucleic acid selected from the group consisting of:

a nucleic acid that specifically hybridizes to a murine ESX nucleic acid under stringent conditions, wherein said murine ESX comprises a nucleic acid sequence as set forth in SEQ ID NO: 15; and

a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 16.

17. (Once amended) The nucleic acid of claim 16, wherein said nucleic acid comprises a nucleic acid that encodes an amino acid sequence of amino acids 2 through 371 of SEQ ID NO: 16.

18. (Once amended) The nucleic acid of claim 17, wherein said nucleic acid comprises a nucleotide sequence as set forth in SEQ ID NO: 15.

19. Canceled.

20. (Once amended) The nucleic acid of claim 16, wherein said nucleic acid comprises a nucleic acid that specifically hybridizes to a murine ESX nucleic acid under

stringent conditions, wherein said murine ESX consists of a nucleic acid sequence as set forth in SEQ ID NO: 15.

21. The nucleic acid of claim 16, wherein said nucleic acid further comprises a vector.

22. The nucleic acid of claim 16, wherein said nucleic acid is labeled.

23. The nucleic acid of claim 22, wherein said nucleic acid is free of dideoxynucleotides.

24. The nucleic acid of claim 22, wherein said nucleic acid is single stranded.

25. The nucleic acid of claim 24, wherein said nucleic acid is a sense strand.

26. The isolated nucleic acid of claim 22, wherein said label is a radionuclide.

27. Canceled..

71. A transfected cell comprising a heterologous gene encoding an ESX transcription factor.

79. A kit for the detection of a ESX gene or polypeptide, said kit comprising a container containing a molecule selected from the group consisting of an ESX nucleic acid or subsequence thereof, an ESX polypeptide or subsequence thereof, and an anti-ESX antibody.

82. (New) The nucleic acid of claim 1, wherein said nucleic acid is labeled with a detectable label.

83. (New) The nucleic acid of claim 82, wherein said detectable label is selected from the group consisting of a radiolabel, an enzyme, a colorimetric label, a magnetic bead, a fluorescent label, and a biotin.